BEST AVAILABLE IMAGES

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images may include (but are not limited to):

- BLACK BORDERS
- TEXT CUT OFF AT TOP, BOTTOM OR SIDES
- FADED TEXT
- ILLEGIBLE TEXT
- SKEWED/SLANTED IMAGES
- COLORED PHOTOS
- BLACK OR VERY BLACK AND WHITE DARK PHOTOS
- GRAY SCALE DOCUMENTS

IMAGES ARE BEST AVAILABLE COPY.

As rescanning documents *will not* correct images, please do not report the images to the Image Problem Mailbox.

B1

OPIC
OFFICE DE LA PROPRIÉTÉ INTELLECTUELLE DU CANADA

CIPO
CANADIAN INTELLECTUAL PROPERTY OFFICE

(12) (19) (CA) **Brevet-Patent**

(11) (21) (C) **2,139,896**
(22) 1995/01/10
(43) 1996/07/11
(45) 2000/03/28

(72) McDonah, Don B., US
(73) Duchesnay Inc., CA

(51) Int.Cl.[6] A61K 31/44

(54) **UTILISATION D'UN AGENT ANTINAUSEEUX CHEZ DES PATIENTS EN PHASE TERMINALE**

(54) **USE OF ANTINAUSEANT AGENT FOR TERMINALLY ILL HUMANS**

(57) Disclosed herein is the use of a mixture of Doxylamine succinate and Pyridoxine HCl (Vitamin B6) in approximately equal weight ratios together with a pharmaceutically acceptable carrier to prevent and suppress the symptoms of nausea and vomiting among terminally ill individuals.

ABSTRACT OF THE DISCLOSURE

Disclosed herein is the use of a mixture of Doxylamine succinate and Pyridoxine HCl (Vitamin B6) in approximately equal weight ratios together with a pharmaceutically acceptable carrier to prevent and suppress the symptoms of nausea and vomiting among terminally ill individuals.

FIELD OF THE INVENTION

The present invention relates to the field of antinauseant agents and their use. More specifically, the present invention relates to the novel use of an antinauseant agent, namely a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios, directed to terminally ill humans.

BACKGROUND OF THE INVENTION

Nausea is probably the second most frequently encountered symptom in the management of people approaching death. It is second only to pain. Nausea is a poorly understood condition which may be subjectively described as the unpleasant feeling of the need to vomit and is often accompanied by other symptoms such as dizziness, vertigo, chills and sweating. It has a wide range of effects ranging from being a mild nuisance to a severely debilitating problem.

It is generally agreed that the vomiting control zone in the human body in situated in the brain stem. This vomiting centre has a direct effect on the gut. The vomiting centre is understood to be affected by various sources such as:

(i) local receptors in the gut during digestion, local irritation by medications or alcohol;

(ii) the vestibular apparatus as stimulated by motion, sight, smell and taste;

(iii) the cerebral cortex as stimulated by stress or other psychological factors such as anxiety disorders;
(iv) increased intra-cranial pressure associated with brain tumours;
(v) the chemoreceptor trigger zone (CTZ), situated in the medulla of the brain stem and having direct link to the vomiting centre.

For terminally ill patients, pain control often requires the use of various pain killers such as narcotics which will stimulate the CTZ. Chemotherapy agents are also generally known to stimulate the CTZ. This will often trigger nausea because of its effect of the vomiting centre. Accordingly, both the drug therapy and the disease afflicting the terminally ill patient contribute to the debilitating symptoms of nausea.

A number of classes of antinauseant agents are known to work with varying degrees of success for terminally ill humans. One important drawback with most known antinauseant agents are their unwanted side effects. Another drawback is that many patients will fail to respond to traditional antinauseant agents used in palliative care.

One class of known antinauseant are the phenothiazines. These act mainly as dopamine antagonists, in other words by blocking the dopamine receptors in the CTZ. However, they also have sedating properties, may cause confusion and have other extra-pyramidal side effects such as low blood pressure,

negative cardiac effects, mobility decrease effects. Consequently, this medication should not be used for severely depressed patients, those with liver disease, renal insufficiency, important cardiovascular disorders or Parkinson's disease. The two most commonly used phenothiazines are Prochlorperazine (sold as Stemetil™) and Haloperidol (sold for example as Haldol™, Novo-Peridol™).

Another class of antinauseant medication are the upper gastro-intestinal motility agents. One such agent is Metoclopramide HCl (sold as Maxeran™) which acts both on the gut and centrally by crossing the blood brain barrier to block dopamine receptors in the CTZ. It is particularly indicated for patients undergoing chemotherapy. Among their side effects profile is inducing confusion, especially among elder patients. Two other gastro-intestinal motility agents are Domperidone maleate (sold as Motilium™) and Cisapride (sold as Prepulsid™). However, these latter two agents do not cross the blood brain barrier to block dopamine receptors in the CTZ. Their side effects profile includes confusion.

Another class of antinauseant agent is Nabilone (sold as Cesamet™) which is a marijuana derivative. Its mechanism of action is not quite understood. Although it may be quite effective for some patients, it is accompanied by side effects which may be distressing to

the patient, such as drowsiness, vertigo and psychotropic effects.

Dexamethazone (sold as Decadron™ or Dexasone™) is another class of agent used on occasion to treat the symptoms of nausea and vomiting. It works quite well for patients having increased intercranial pressure resulting from for example brain tumours. It is believed to help in chemotherapy induced nausea and vomiting by what appears to be a decrease in cerebral edema which may occur around both the CTZ and the vomiting centre.

Antihistamines are commonly used in nausea and vomiting but are generally less effective than phenothiazines. The most common antihistamine nausea medication is Gravol™. They are known to work well in nausea and vomiting related to vestibular stimulation and may, in some instances, have a sedating effect.

Benzodiazepines are another class of agents sometimes used as antinauseants. They are felt to work at the cerebral cortex level by decreasing anxiety and other psychological disorders.

Consequently, there remains a need for an improved antinauseant agent showing minimal or no side effects and effective in a palliative care setting where the symptoms associated with nausea and vomiting are particularly debilitating. The need is exacerbated where the traditional antinauseant agents bear a number of unwanted side effects or are merely effective for some sources of nausea and vomiting. The need is also

exacerbated when the patient is not responsive or only partially responsive to traditional palliative care antinauseant agent.

Another class of antinauseant agent, not previously used in palliative care but rather for treating the symptoms of morning sickness among pregnant women and, in some extreme cases hyperemesis gravidarum, consists of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight. This antinauseant agent is currently available under the trademark Diclectin™. So far, the use of Diclectin™ has been restricted to the treatment of the specific forms of nausea and vomiting among pregnant women such as hyperemesis gravidarum and morning sickness. Prior to the present invention, it was not known nor predictable that a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight could be effectively used in a palliative care setting to treat the nausea and vomiting associated with chemotherapy, pain-killing pharmacological therapy, various terminal diseases and conditions. Indeed, the physiological and therapeutical causes of nausea and vomiting encountered in a palliative care setting are completely different from the causes of nausea and vomiting among pregnant women which are generally thought to be related to hormonal changes during pregnancy.

Accordingly, it is an object of the present invention to divulge a novel use for a mixture of

Doxylamine succinate and Pyridoxine HCl in approximately equal weight, namely for the treatment of the symptoms of nausea and vomiting among terminally ill humans.

Other objects and further scope of applicability of the present invention will become apparent from the detailed description given hereinafter. It should be understood, however, that this detailed description, while indicating preferred embodiments of the invention, is given by way of illustration only, since various changes and modifications within the spirit and scope of the invention will become apparent to those skilled in the art.

SUMMARY OF THE INVENTION

The invention provides the use of a therapeutically effective amount of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight for preventing and suppressing the symptoms of nausea and vomiting in terminally ill humans.

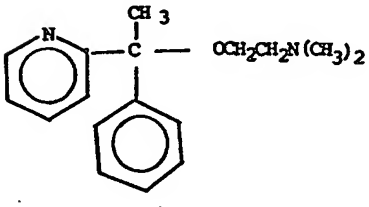
In a preferred embodiment, the use of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight is directed to patients undergoing chemotherapy.

In other embodiments, the use of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight is directed to patients suffering from cancer or from Acquired Immunity Deficiency Syndrome (A.I.D.S.).

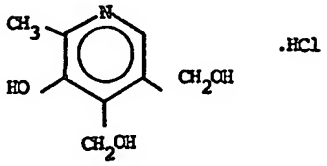
Other features and advantages of the invention will become apparent to those of ordinary skill in the art upon review of the following detailed description and claims.

DETAILED DESCRIPTION

Diclectin™ consists of a mixture of two pharmaceutical substances in approximately equal proportions together with a pharmaceutically acceptable carrier. The two pharmaceutical substances are Doxylamine succinate, an antihistamine, and Pyridoxine HCl, which is Vitamin B6. The shorthand chemical formulas of the substances are illustrated below:



Doxylamine succinate



Pyridoxine HCl

The precise mechanism of how Diclectin™ is effective for treating the symptoms of morning sickness and hyperemesis gravidarum remains unknown. It is generally agreed that there is a synergistic effect between the two active ingredients found in Diclectin™. Diclectin™ is known to be prescribed in delayed release tablet form; each tablet

containing 10mg of each of Doxylamine succinate and Pyridoxine HCl, for pregnant women suffering from the symptoms of morning sickness or hyperemesis gravidarum during the first few weeks of pregnancy. The dosage is usually 1-4 tablets daily.

Diclectin™ is not known as a general antinauseant agent. However, it was surprisingly found that Diclectin™ can be used for effectively controlling the symptoms of nausea and vomiting experienced by terminally ill patients without the debilitating side-effects encountered with other antinauseant agents, such side effects as trembling, low blood pressure, mobility decrease, rigidity, negative cardiac effects, confusion, vertigo, etc. It was also surprisingly found that when patients poorly responded to other antinauseant agents traditionally used for patients suffering from a terminal illness, those patients often did respond to Diclectin™. It was also surprisingly found that following examples given for illustrative purposes demonstrate the novel use of Diclectin™ among terminally ill patients suffering from excessive nausea and vomiting.

EXPERIMENTAL

The following examples are given solely for illustrative purposes and to demonstrate the novel use of Diclectin™ among terminally ill patients suffering from excessive nausea and vomiting.

Example 1

A female patient, 50 years of age, had an advanced form of colon carcinoma. At the time of diagnosis, the carcinoma was disseminated through her pelvis and abdomen. She suffered from pain but also from extreme and debilitating nausea and vomiting. Her nausea and vomiting had forced her to remain hospitalized for extended periods of time although the rate of progression of her disease would have allowed to perform some normal activities for a few months. She was poorly responsive to traditional antinauseants such as gastro-intestinal motility agents, for example, Maxeran™ or Motilium™ or phenothiazines. Diclectin™ was then administered to her in an effort to control her nausea and vomiting. She took 40mg in tablet form at night and 20mg also in tablet form in the morning. She showed a dramatic improvement and was, a short while later, able to go home and resume some normal activities by taking Diclectin™ for approximately four months. She was even able to enjoy her sailboat a few times during that summer. It is noted that at one point during her Diclectin™ therapy, feeling better, she attempted to discontinue the use of Diclectin™ only to find a resurgence of her nausea and vomiting. She resumed taking Diclectin™ and was soon cleared again of her nausea and vomiting problem.

Example 2

A male patient, 74 years of age, diagnosed with carcinoma of the prostate and metastatic disease to his bones. Not only did he experience pain but he had a severe problem of nausea. He would be nauseated upon waking up to about noon and would then feel somewhat better as the day went on. It was not determined why the patient was nauseated. He was poorly responsive to traditional antinauseants. Diclectin™ was administered to him in small doses of 20mg. In the space of approximately 4 days, he showed a dramatic improvement. He was not able to leave the hospital because of the advanced state of his disease but during the two weeks prior to his death, he was able to take fluids and did not experience that terrible feeling of nausea which had afflicted him prior to taking Diclectin™.

Example 3

A female patient, diagnosed with breast cancer. She frequently was plagued by bouts with nausea and vomiting. She was initially treated with a phenothiazines (Stemetil™) to which she responded poorly because of the adverse side extra-pyramidal reactions including tremor, rigidity, etc. which made her appear to be developing Parkinson's disease. The phenothiazine therapy was discontinued and replaced by Diclectin™.

Shortly thereafter, in the space of approximately one week, the patient's nausea was controlled and the extra-pyramidal effects of the previous medication were gone.

Although the invention has been described above with respect with one specific form, it will be evident to a person skilled in the art that it may be modified and refined in various ways. It is therefore wished to have it understood that the present invention should not be limited in scope, except by the terms of the following claims.

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. The use of a therapeutically effective amount of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios for preventing and suppressing the symptoms of nausea and vomiting in terminally ill humans.

2. An oral medicament comprising a therapeutically effective amount of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios together with pharmaceutically acceptable carrier for use in preventing and suppressing the symptoms of nausea and vomiting in terminally ill humans.

3. A rectal suppository medicament comprising a therapeutically effective amount of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios together with pharmaceutically acceptable carrier for use in preventing and suppressing the symptoms of nausea and vomiting in terminally ill humans.

4. An intravenous medicament comprising a therapeutically effective amount of a mixture of Doxylamine succinate and Pyridoxine HCl in approximately equal weight ratios together with pharmaceutically acceptable carrier for use in preventing and suppressing the symptoms of nausea and vomiting in terminally ill humans.

5. The use of claim 1 wherein said terminally ill humans suffer from cancer.

6. The use of claim 1 wherein said terminally humans suffer from acquired immunity deficiency syndrome (A.I.D.S.).

7. The medicament of any of claims 2 to 4 wherein said terminally ill humans suffer from cancer.

5

8. the medicament of any of claims 2 to 4 wherein said terminally ill humans suffer from acquired immunity deficiency syndrome (A.I.D.S.).